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Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis

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Aims There is no agreement in the best cutoff time to distinguish between early- and late- onset prosthetic valve endocarditis (PVE). Our objectives are to define early-onset PVE according to the microbiological spectrum and to analyse the profile and short-term prognosis of this entity.
Methods and results The microbiological profile of 172 non-drug users, who were patients with PVE, were compared according to the time elapsed from surgery among 640 endocarditis diagnosed between 1996 and 2004. There were no differences in the microbiological profile of patients with PVE occurred within 2 months of valve replacement and those accounting between 2 and 12 months. The proportion of coagulase-negative *Staphylococci* (CNS) was higher during the first year post-intervention (37 vs. 18%, $P = 0.005$) and *Streptococci viridans* were more common after 1 year (18 vs. 1%, $P = 0.001$). The percentage of methicilin-resistant CNS strains was higher before 1 year (77 vs. 30%, $P = 0.004$). Early-onset PVE represented 38% of all episodes of PVE, CNS being the most frequent isolated microorganisms (37%), most of them methicilin resistant (77%). In-hospital mortality of patients who needed urgent surgery was 46% and elective surgery 25%. Overall, in-hospital mortality was 38% and no differences were seen between surgical and medical groups (32 vs. 45%, $P = 0.30$). Periannular complications were associated with higher in-hospital mortality (60 vs. 27%, $P = 0.007$).
Conclusion According to the microbiological profile, the most appropriate cutoff time to distinguish between early- and late-onset PVE was 1 year. Methicilin-resistant CNS are the most frequent pathogens and periannular complications, the only risk factor for in-hospital mortality.

Introduction

Despite major advances in cardiovascular surgical techniques and routine use of prophylactic antimicrobial agents, prosthetic valve endocarditis (PVE) continues to complicate the course of a small percentage of patients after cardiac valve replacement. Its incidence is highest within 12 months of valve replacement and ranges between 1.4 and 3.1%.[1,2] Because distinct features in the clinical course exist when comparing early- and late-onset infections, patients with PVE are usually classified in two groups according to the time elapsed from surgery. There is no agreement regarding the cutoff time to classify a PVE as early or late. Some authors consider 1 year,[3–7] others 60 days[2,8–14] after the surgery, and others distinguish between early-, intermediate-, and late-onset PVE (LO-PVE).[15,16] We present a multicentre study with uniform data collection, prospective inclusion of patients, strict definitions of endocarditis, and widespread use of transeophageal echocardiography (TEE) to (i) define the microbiological profile over time to subsequently define the most appropriate cutoff time, (ii) evaluate the clinical, echocardiographic, microbiological, and prognostic profile of early-onset PVE (EO-PVE).

Methods

Patient population

This study was conducted at five tertiary care centres with surgical facilities and involved all consecutive cases of infective endocarditis diagnosed at our centres between 1996 and 2004. To ensure consecutive enrolment, all patients who underwent echocardiography in whom endocarditis was suspected were observed until a diagnosis was established. Patients with a final diagnosis of endocarditis were included in the study. A standardized case report form with 10 epidemiological, 10 clinical, nine analytical, three radiographic, four electrocardiographic, 10 microbiological, and 13 echocardiographic variables was used by all participant centres and all patients were registered on an on-going database.

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We have compared the microbiological spectrum according to the time elapsed from surgery (<2 vs. 2–12 months and <12 vs. >12 months) in order to determine the best cutoff time to distinguish between EO- and LO-PVE. Then, we have described the epidemiological, microbiological, echocardiographic, and evolutive characteristics of EO-PVE and compared the demographic profile of EO- and LO-PVE to determine if there are factors affecting the diferent microbiological characteristics between both entities. Finally, we have analysed the prognostic factors of in-hospital mortality of patients with EO-PVE.

Definition of terms and protocol

Table 1 shows the definitions used throughout the study. Indications for urgent surgery were consesuated by the investigators before the design of the study and included heart failure with prosthetic valve dysfunction, fungal endocarditis, bactereamia or fever after 7 to 10 days of appropriate antibiotic therapy without non-cardiac causes for bacteraemia, and recurrent peripheral embolus despite therapy. All patients underwent transthoracic (TTE) and TEE. The echocardiographic demonstration of a periannular complication was not considered an indication for surgery *per se*. In-hospital mortality was defined as death occurring during the initial hospitalization for infective endocarditis independently of the aetiology.

Statistics

All data for analysis were entered into a computer database SPSS V12.0 (SPSS Inc. Chicago, IL, USA). The Shapiro–Wilk test was used to verify the normality of distribution of continuous variables. The results of normal distributed data were expressed as mean ± SD, whereas non-normally distributed data were expressed as median and inter-quartile range. Comparisons were carried out using the Student's *t* test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed data. Qualitative variables were expressed as count and percentages and compared with χ^2 test or Fisher's exact test when necessary. Significance was set at a probability (*P*) of <0.05.

Table 1 Definitions of terms

Terms	Definitions
Nosocomial endocarditis	Endocarditis acquired more than 3 days after hospital admission with no clinical manifestations of endocarditis before admission
Acute onset	Span of time between onset of symptoms and admission to the hospital shorter than 15 days
Atrioventricular block	First, second, or third degree atrioventricular block
Renal failure	Serum creatinine equal or higher than 2 mg/dL
Heart failure	Diagnosis according to accepted criteria[29]
Embolic events	Diagnosis based on clinical signs and data derived from non-invasive diagnostic procedures
Urgent surgery	Surgery performed prior to the completion of the standard course of antibiotic therapy
Elective surgery	Surgery performed after finishing the antibiotic regimen
Abscess[30,31]	Well-delineated perivalvular area of reduced echodensity with no flow
Pseudoaneurysm	Echo-free perivalvular pouch with flow in its interior
Fistula	Narrow communication between two adjacent chambers

Results

Justification of the cutoff time

No differences in the microbiological profile of patients with PVE occurred within 2 months of valve replacement and those accounting between 2 and 12 months were seen (*Figure 1A*). Nonetheless, the microbiological profiles of PVE during and after 1 year were clearly different (*Figure 1B*). The proportion of coagulase-negative *Staphylococci* (CNS) was higher during the first year post-intervention (37 vs. 18%, $P = 0.005$); on the other hand, *S. viridans* were more common causes of PVE after 1 year (18 vs. 1%, $P = 0.001$). Furthermore the percentage of methicilin-resistant CNS strains was higher in PVE before 1 year (77 vs. 30%, $P = 0.004$).

Clinical characteristics

A total of 640 episodes of endocarditis according to the Duke criteria[17] were registered in non-drug users between 1996 and 2004, and 172 were prosthetic: 66 (63 definite and three possible) had been acquired in the first year post-implantation and were left-sided (38%). The mean interval between the valve operation and the onset of signs and symptoms of endocarditis was 129 days (range 4–328 days).

Mean age was 59 years (range 28–82 years) and the male–female ratio was 1:1. The percentage of patients older than 70 years was 21%. The acquisition was nosocomial in 41 cases (62%), previous endocarditis had occurred in 11 (17%), and 18 were referred from other centres (27%). A pre-existing underlying condition was present in 24 patients (36%) (*Table 2*).

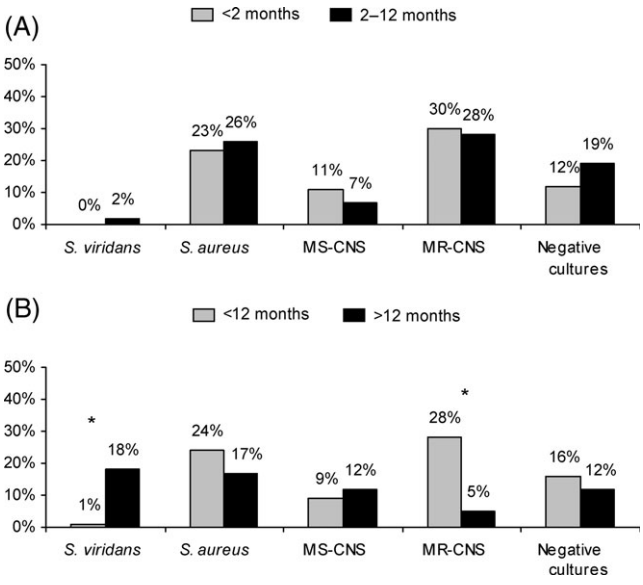

Figure 1 (*A*) Comparison of the microbiological profile of PVE within 2 months of valve replacement ($n = 25$, 27 microorganisms) and between 2 and 12 months ($n = 41$, 44 microorganisms). (*B*) Comparison of the microbiological profile of PVE within 12 months of valve operation ($n = 66$, 71 microorganisms) and after 12 months ($n = 106$, 115 microorganisms). MR, methicilin resistant; MS, methicilin sensitive; *$P < 0.05$.

Table 2 Predisposing conditions for endocarditis in 24 patients. Ten patients had more than one predisposing condition

Diabetes mellitus	10 (15%)
Chronic renal insufficiency	8 (12%)
Chronic anaemia	5 (8%)
Immunodepression	5 (8%)
Cancer	2 (3%)
Alcoholism	1 (2%)
Immunodepresive treatment	1 (2%)
Colagenopathy	2 (3%)

Fever was the most frequent initial symptom (48 patients, 73%). During admission, 33 patients had dyspnoea, three skin manifestations, and seven splenomegally. During the course of the disease, 35 patients (53%) developed heart failure (11 class III and 10 class IV NYHA), 26 renal insufficiency (39%), 13 stroke (20%), (nine ischaemic and four haemorrhagic), 17 systemic embolism (26%), and seven septic shock (11%).

The chest radiograph showed heart enlargement in 48 patients (73%), pulmonary congestion in 25 (38%), and pleural effusion in 20 (30%). An atrioventricular block was detected in 11 cases (17%).

Microbiological findings

Blood cultures were positive in 55 patients (83%). None of the remaining 11 had positive results in the serology against *Clamydia*, *Mycoplasma*, and *Legionella* and six had been under antibiotic treatment before blood samples were obtained. CNS and *S. aureus* were the most frequent isolated microorganisms. The majority of CNS (77%) were methicilin resistant. The complete distribution of causative microorganisms is shown in *Table 3*.

Echocardiographic findings

Endocarditis affected mechanical prosthesis in mitral position in 33 patients (47%), 29 aortic mechanical prosthesis (41%), five aortic bioprosthesis (7%), and three mitral bioprosthesis (4%). In four cases, two prosthetic valves were affected. TEE revealed valvular vegetations in 53 patients (82%) (mean diameter $12.9 \times 7.4 \pm 5.8 \times 4.5$ mm; mean area 0.75 ± 0.63 cm^2) and periannular complications in 26 patients (39%): 19 abscesses, 11 pseudoaneurysm, and five fistula (nine patients had more than one periannular complication). Periannular complications were localized in aortic position more frequently than in mitral position but the difference was not statistically significant (52 vs. 31%, $P = 0.083$).

Treatment and outcome

Urgent surgery was needed on 13 patients (eight with heart failure class III/IV, four with uncontrolled infection, and one for recurrent embolic events), elective surgery was performed in 24 patients, and the remaining 29 patients received only medical treatment. Mortality rates associated with each option are shown on *Figure 2*. Among patients treated medically, seven were judged not to be surgical candidates or too ill to undergo an open-heart operation. Overall, mortality was 38% (25 patients), 32% in the surgical group, and 45% in the non-surgical group ($P = 0.30$). Multiorgan failure with severe sepsis was the most frequent cause of mortality (10 patients). Other causes of mortality were heart failure ($n = 7$), stroke ($n = 3$), arrhythmias ($n = 2$), and perioperative complications ($n = 3$).

The most frequent type of intervention was the replacement of the infected prosthesis with a mechanical prosthesis (31 patients), followed by the implantation of a homograft (four patients) and a bioprosthesis (two patients).

Table 3 Microbiological spectrum of the 66 patients (71 microorganisms) with EO-PVE

Infective microorganism	EO-PVE
Coagulase-negative *Staphylococci*	26 (37%)
Staphylococcus aureus	17 (24%)
Enterococci	5 (7%)
Gram negative bacilli	4 (6%)
Fungi	3 (4%)
Anaerobes	3 (4%)
Streptococus bovis	1 (1%)
Streptococci viridans	1 (1%)
Other *Streptococci*	0 (0%)
Negative cultures	11 (16%)

Comparison between the demographic profile of EO- and LO-PVE

In order to determine if there are patient factors of influence on the microbiological profile of PVE, we have compared the demographic profile of both types of PVE. Results are shown in *Table 4*.

Predictors of mortality

A total of 59 epidemiological, analytical, clinical, microbiological, and echocardiographic variables were analysed to find out whether mortality could be predicted. The univariate results of the most clinically meaningful variables are shown in *Table 5*. Remarkably, laboratory findings and microbiological profile did not predict mortality in the univariate analysis.

Discussion

PVE is a quite infrequent disease but has a great impact given the high morbidity and mortality which it bears. It accounts for 27% of all cases of infective endocarditis treated in our centres, a similar proportion to that presented by other groups.[8] Optimal management of patients with infected prosthetic cardiac valves represents a challenge for both physicians and surgeons. The most appropriate treatment approach of PVE, either medical or surgical, is still a matter of debate because no randomized, controlled studies had been undertaken.

ACC/AHA[18] and the European guidelines[19] advocate surgery for EO-PVE (indication class I) but reviewing most series in the literature, the degree of fulfillment of this indication is low.[2–16] Ours and other investigators[3,7,11,13,20] show that there is no clear evidence that all patients with EO-PVE should be treated surgically on a systematic basis, because

there are patients with good prognosis who can undergo medical treatment alone. We do believe that this decision must be individualized and many factors have to be taken into account.

PVE have been classically classified into two groups (EO- and LO-PVE) according to the time elapsed from the valve substitution to the onset of symptoms. There is no agreement in the cutoff time and it is often arbitrarily established. Conceptually, EO-PVE are acquired in the peri-operative period (in the operatory room or in the immediate

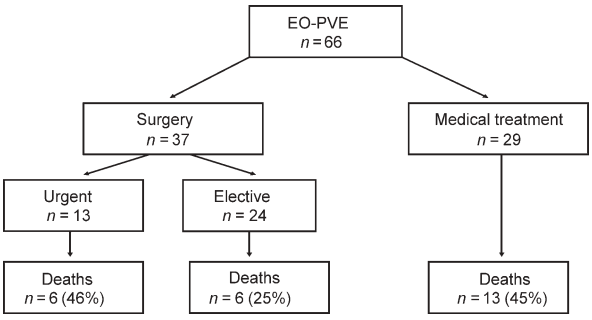

Figure 2 Treatment options and associated mortality.

Table 4 Comparison demographic profile of PVE within 12 months of valve operation and after 12 months

	EO-PVE ($n = 66$)	LO-PVE ($n = 106$)	*P*-value
Age (years)	59 ± 13	62 ± 12	0.124
Male gender	33 (50%)	64 (60%)	0.182
Referred	18 (27%)	40 (38%)	0.158
Nosocomial acquisition	41 (62%)	25 (24%)	<0.001
Intravenous drug users	1 (2%)	1 (1%)	0.999
VIH	1 (2%)	0 (0%)	0.384
Comorbid conditions	24 (36%)	52 (49%)	0.103
Diabetes mellitus	10 (15%)	29 (27%)	0.063
Chronic renal insufficiency	8 (12%)	13 (12%)	0.978
Chronic anaemia	5 (8%)	15 (14%)	0.191
Dermathopaty	0 (0%)	2 (2%)	0.524
Colagenopathy	2 (3%)	0 (0%)	0.146
Immunocompromised state	7 (11%)	4 (4%)	0.108
Cancer	2 (3%)	7 (7%)	0.485
Alcoholism	1 (2%)	1 (1%)	0.999
Previous endocarditis	11 (17%)	22 (21%)	0.508

Table 5 Prognostic factors: univariate analysis

	Survivors ($n = 41$)	Deaths ($n = 25$)	*P*-value
Age (years)	59 ± 14	61 ± 13	0.545
Male gender	21 (51%)	12 (48%)	0.800
Referred	12 (30%)	6 (24%)	0.810
Nosocomial acquisition	25 (68%)	16 (64%)	0.986
Comorbid conditions	14 (34%)	10 (40%)	0.829
Previous endocarditis	5 (12%)	6 (24%)	0.308
Clinical manifestations at admission			
Acute onset	23 (56%)	17 (68%)	0.484
Fever	26 (63%)	22 (88%)	0.059
Hematological findings			
Serum creatinine (mg/dL)[a]	1.1 (0.95–1.3)	1.0 (0.9–1.9)	0.901
Electrocardiographic findings			
Atrioventricular block	5 (12%)	6 (24%)	0.308
Clinical complications			
Heart failure	21 (51%)	14 (56%)	0.706
Stroke	7 (17%)	6 (24%)	0.535
Peripheral embolus	10 (24%)	7 (28%)	0.972
Septic shock	2 (5%)	5 (20%)	0.095
Renal failure	13 (32%)	13 (52%)	0.169
Microbiological findings			
Coagulase-negative *Staphylococci*	20 (44%)	6 (24%)	0.171
Staphylococcus aureus	9 (20%)	8 (32%)	0.378
Gram negative bacilli	4 (9%)	0 (0%)	0.290
Negative cultures	7 (15%)	4 (16%)	0.999
Echocardiographic findings			
Valve involved			0.254
Aortic mechanical prothesis	14 (34%)	11 (44%)	
Mitral mechanical prothesis	24 (59%)	9 (31%)	
Aortic bioprosthetis	2 (5%)	3 (10%)	
Mitral bioprosthetis	1 (2%)	2 (7%)	
Presence of vegetations	31 (76%)	22 (88%)	0.340
Periannular complications	11 (27%)	15 (60%)	0.007
Ejection fraction	57.6 ± 14.5	59.3 ± 10.9	0.661

[a]Median (interquartile range).

post-operative period throughout the infection of incisions, central catheters, urinary probes, etc). LO-PVE are acquired in the community and the microbiological profile mirrors of native valve endocarditis. Therefore, the difference between EO- and LO-PVE should be based on microbiological aspects rather than on the time elapsed from surgery. According to differences in the microbiological profile, we have found the cutoff time of 1 year after operation to be the most appropriate. Moreover, the only difference in the demographic profile of EO- and LO-PVE was that nosocomial acquisition was more frequent between EO-PVE.

The microorganisms responsible for EO-PVE in our study were similar to previous reported series.[3–5,9,14,21] The pathogen profile of EO-PVE is dominated by *Staphylococcal* species (coagulase-negative and *S. aureus)* accounting for 37 and 24% of cases, respectively, even though prophylactic regimens used today in cardiac surgery are targeted against these microorganisms.[22,23] Interestingly, the majority of infections caused by CNS were resistant to methicilin (77%), which is a strong argument suggesting the nosocomial origin of many PVE occurring during the first year after valve replacement.

Studies addressing the outcome of PVE have been retrospective,[4,5,9] come from a single institution,[4] and consider different times for outcome assessment. Our work is unique in several ways: (i) it is a multicentre study; (ii) our patients were consecutively and prospectively included; (iii) all patients underwent TEE; (iv) a uniform data collection and diagnostic and therapeutic criteria have been used from the beginning of the study; (v) a large number of variables has been analysed; and (vi) strict definitions of endocarditis and complications have been used.

Periannular complications were very common in our population, with a proportion similar to that described in previous studies.[16] TEE is clearly better than TTE in the diagnosis of periannular complications with sensitivity and specificity rates of 87 and 95% for TEE, which compares favourably with 28 and 99% for TTE.[24] One of the most relevant findings of our work is that periannular complications were the only factor associated with higher in-hospital mortality rates in our patients. They have been already identified as predictors for surgical recurrence[12] and worse long-term prognosis,[25,26] but this is the first study to report periannular complications as predictors for in-hospital mortality in patients with EO-PVE. Keeping these considerations in mind, it seems wise to perform TEE on every patient with EO-PVE.

Our rate of complications, surgery, and in-hospital mortality rates are similar to that reported by other authors[3,6,8,10] and lower than described in classical text books,[27,28] which could be explained by the advance in the diagnosis, detection, and earlier treatment of complications of the disease experimented in the last decades.

The low use of homografts in our series (only 11%) is explained by the unavailability to obtain them on an urgent basis. In fact, homographs were not used in any patient who required urgent surgery. Regarding the low use of bioprosthesis, we followed the same criteria irrespective of whether the patient has endocarditis or non-infectious valvular disease. Only three of patients were older than 70 and a bioprosthesis was implanted in two of them.

We are aware of potential weaknesses of the present study. First, this is an observational study and allocation of therapies was not randomized. Thus, bias in the selection of therapies was present. Second, ours are large reference centres that obviously introduce a bias in the patients included in our database. Thus, our conclusions are pertinent to tertiary care centres with surgical facilities and cannot be generalized. Nevertheless, it has to be agreed that every patient with EO-PVE should be treated in a hospital of this nature. Finally, another drawback is the limited number of patients included which make our conclusions not definite; to our knowledge, however, it is one of the largest recent series published in the literature and our results may contribute in the better understanding of this devastating disease.

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Conflict of interest: none declared.

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